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Medical Information

Chelation Therapy

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This statement was prepared in response to a request made to the Clinical Pharmacology Service at the University of California, San Francisco to evaluate the potential therapeutic uses and the possible toxicities of chelation therapy. The question arose in regard to the use of ethylene tetraacetic acid (EDTA) in the treatment of atherosclerotic cardiovascular disease.

Action

Disodium edatate (Na_2 EDTA or edathamil or versenate) is a complex molecule whose only recognized pharmacologic action is the chelation of certain divalent and trivalent cations (such as calcium, zinc, cadmium, mangnanese, lead, vanadium and plutonium). Following oral administration, 80 to 95 percent of the dose appears in the feces within 24 hours. After intravenous administration, 95 percent of the dose appears in the urine by 24 hours and less than 0.5 percent remains in the body after 48 hours. The compound is not metabolized and is handled by the kidneys as inulin is, so that alterations in urine flow rate and pH do not affect overall excretion rate of EDTA, although impaired renal function with reduced glomerular filtration will delay excretion.[1]

Disodium-EDTA administered parenterally binds serum calcium very rapidly, and administration rates greater than 15 mg per minute produce hypocalcemic tetany. Slower rates do not affect serum calcium levels, but mobilize bone calcium and induce hypercalcuria. (Calcium-Na_2 EDTA does not affect plasma or body levels of calcium, but otherwise has the same actions and toxicities as the unchelated form).[1]

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Accepted Therapeutic Uses and Doses

The single, generally recognized use of EDTA is in the diagnosis and treatment of lead poisoning.[1-4] Other reported and suggested uses are in the diagnosis of hypoparathyroidism, the treatment of porphyria, scleroderma, hypercholesterolemia, hypercalcemia, calcific cardiac valvular disease, cardiac arrhythmias and atherosclerotic coronary artery and peripheral vascular disease.[1,2] Most of these uses are considered "investigational."[2]

Recommended chelation therapy in acute lead intoxication includes the combined parenteral administration of 2,3 dimercaptopropanol (BAL) and Ca EDTA, the latter in doses of 50 to 75 mg per kg of body weight per day for five days, followed by long-term oral therapy with D-penicillamine.[5] The dose of Ca EDTA should exceed 50 mg per kg of body weight per day only when combined with BAL, and even using the recommended dosage schedule, the following side effects have been observed: fever, hypercalcemia, proteinuria, microscopic hematuria and large epithelial cells in the urinary sediment. Therefore, frequent urinalyses and determination of serum electrolytes, blood urea nitrogen, calcium, phosphate and alkaline phosphatase are recommended during therapy.[5] Long-term therapy is considered unwarranted because of potential renal toxicity.[6]

Toxicity

Fatal and nonfatal renal toxicity in humans given large doses of EDTA has been well documented. Reported symptoms include nocturia, frequency and urgency of urination and dysuria. Results of urinalyses have shown albumin, parenchymal cells, granular casts and red and white blood cells. In two fatal cases reported, severe renal tubular damage and widespread engorgement of reticuloendothelial cells were noted at autopsy.[7,8]

Well-designed experimental studies using rats showed that Ca EDTA caused severe hydropic degeneration of proximal tubules, with casts and epithelial cells in urine, that was clearly dose dependant.[7] Other tissues were not affected. The ED-50 (the dose required to produce the first histologic evidence of damage in 50 percent of

animals treated daily for 16 days) was 203 mg per kg of body weight per day. Lesions developed in none of the animals given 62.5 mg per kg of body weight per day for 16 days. Neither acidification nor alkalinization of the urine affected the development of lesions.[7] These studies form the major basis for the dose recommendations in man: not more than 5 grams (70 mg per kg of body weight) per day for not more than five days, followed by a two-day rest period.

Other toxicities reported include thrombophlebitis (probably related to concentration of the solution); hypocalcemia after rapid administration of disodium EDTA; systemic symptoms of malaise, fatigue, thirst, fever, then myalgia and headache in a characteristic sequence often heralding renal toxicity; histamine-like reactions; glycosuria without a diabetic state; anemia in one case; dermatitis similar to that seen with avitaminosis B, especially B_6;[9,10] and fatal emboli in a patient with calcium deposits in heart valves.[11] Congenital malformations and fetal deaths were consistently observed after administration of EDTA to pregnant rats; these changes were prevented by administration of zinc.[12]

Use in Atherosclerotic Cardiovascular Diseases

In 1955, a case report regarding EDTA therapy in a patient with severe nephrocalcinosis states, on the basis of serial x-ray films of the abdomen, that there was a 50 to 65 percent decrease in renal metastatic calcium following prolonged therapy with intravenously given EDTA totalling 575 grams in 13 months; neither renal function, nor side effects were reported.[13]

The same authors reported dissolution of mitral valve calcification and relief of congestive pulmonary symptoms following EDTA therapy in a patient with rheumatic heart disease, and removal of metastatic calcium from a necrotic sinus tract in a patient previously operated on for thyroid malignancy.[11] Extrapolating from these experiences, the authors reported treating 20 patients with progressive angina pectoris with prolonged courses of EDTA (5 grams daily for five days, followed by a two-day rest period, to a total of 75 to 300 grams).[11] Results were reported in terms of subjective symptomatic improvement. Also of 17 patients with abnormal findings on electrocardiograms, six were stated to have improved; and electrocardiograms from two patients were displayed, but the improvements were difficult to interpret. One patient died following a convulsion; results of autopsy showed extensive aortic atheromatosis and it was suspected "that he died from a calcium embolus that had been freed from a large arterial plaque." No other toxicities were apparently monitored nor commented upon.[11]

Results of a third study, involving ten men with disabling angina pectoris, were also reported in terms of subjective symptomatic improvement and changes noted on electrocardiograms, without mention of toxicities.[14] No well designed, controlled studies with blindly read, objective results have been reported.

Because of the risk of severe renal toxicity, and the lack of objective evidence suggesting therapeutic benefit from EDTA therapy for atherosclerotic disease, such therapy should be regarded as investigational and conducted under carefully controlled conditions in an academic institution by experienced investigators.

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